FIGURE 1

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```
GGATCCCCTGCTCCAGCAGCTGCAAGGTGCAAGAAGAAGAAAGATCCCACCGAGGAAAATGTG  120
                                                          M  C    2
CTGGAGACCCCTGTGTCGGTTCCTGTGGCTTTGGTCCTATCTGTCTTATGTTCAAGCAGT  180
 W  R  P  L  C  R  F  L  W  L  W  S  Y  L  S  Y  V  Q  A  V   22
GCCTATCCAGAAAGTCCAGGATGACACCAAAACCCTCATCAAGACCATTGTCACCAGGAT  240
 P  I  Q  K  V  Q  D  D  T  K  T  L  I  K  T  I  V  T  R  I   42
CAATGACATTTCACACACGCAGTCGGTATCCGCCAAGCAGAGGGTCACTGGCTTGGACTT  300
 N  D  I  S  H  T  Q  S  V  S  A  K  Q  R  V  T  G  L  D  F   62
CATCTTTGGGCTTCACCCCATTCTCAGTTTGTCCAAGATGGACCAGACTCTGGCAGTCTA  360
 I  F  G  L  H  P  I  L  S  L  S  K  M  D  Q  T  L  A  V  Y   82
TCAACAGGTCCTCACCAGCCTGCCTTCCCAAAATGTGCTGCAGATAGCCAATGACCTGGA  420
 Q  Q  V  L  T  S  L  P  S  Q  N  V  L  Q  I  A  N  D  L  E  102
GAATCTCCGAGACCTCCTCCATCTGCTGGCTTTCTCCAAGAGCTGCTCCCTGCCTCAGAC  480
 N  L  R  D  L  L  H  L  L  A  F  S  K  S  C  S  L  P  Q  T  122
CAGTGGCCTGCAGAAGCCAGAGAGCCTGGATGGCGTCCTGGAAGCCTCACTCTACTCCAC  540
 S  G  L  Q  K  P  E  S  L  D  G  V  L  E  A  S  L  Y  S  T  142
AGAGGTGGTGGCTTTGAGCAGGCTGCAGGGCTCTCTGCAGGACATTCTTCAACAGTTGGA  600
 E  V  V  A  L  S  R  L  Q  G  S  L  Q  D  I  L  Q  Q  L  D  162
TGTTAGCCCTGAATGCTGAAGTTTCAAAGGCCACCAGGCTCCCAAGAATCATGTAGAGGG  660
 V  S  P  E  C  *                                             167
AAGAAACCTTGGCTTCCAGCCCTCTTCAGCACAACACAGCCCATGTGCACACATCCATCAT  720
TCATTTCTCTCCCCTCCTGTACACCACCCATCCAAAGGCATGACTCCACAATGCTTGACTC  780
AAGTTATCCACACAACTTCATGAGCACAAGGAGGGGCCCAGCCTGCACACCCCACTCTCAC  840
CTAGTTCTTCAGCAAGTAGAGATAAGACCCATCCCATCCCCTCCATGTCCCACCTGCTCC  900
GGGTACATGTTCCTCCGTCCGTACACCCTTCGCTGCGGCCCAGGAGAGGTGAGGTAGGGA  960
TGGGTAGAGCCTTTGGGCCTCTCTCACAGTCTTTGGGAGCACCGTGAAGGCTGCATCCACA 1020
CACAGCTCGAAACTCCCAAGCAGCACACGATGGAAGCACTTATTTATTTATTCTCCATTC 1080
TATTTTGCATGGATCTGAAGCAAGGCATCAGCTTTTTCACGGCTTTGGGGCTCAGCCAGGA 1140
TCAGGAAGGCTCCTGGGGTGCTGCTTTCAATCCTATTCATGCGTCTGCCCGAGGCAAACC 1200
TAATTTTTGAGTGACTGGAAGGAACGTTCCCATCTTCCAAACAAGAGTCTATGCAGGTAG 1260
CGCTCAAGATTGACCTCTGGTCACTGGTTTTGTTTCTATTGTGACTGACTCTATCCAAAC 1320
ACGTTTGCAGCCCCCATTGCCGGGAGCATAGGCTAGGTTATTATCAAAACCAGATGAATTT 1380
TCTCAACTGTAATATGTATCTATGTGCACCTGAGCCTACAGCATGTGTTAGAGGGAGGGT 1440
GAAGGATCCGGAAGTGTTCTCTCAATTACATATGTGTGGTAGGCTTTTCTGAAACGGTGA 1500
GGCATTTTCTTACCTCTGTGGCCACATAGTGTGGCTTTGTGAAAACGACAAAGGAGTTGA 1560
CTCTTTCCCCGAACATTTGGAGTGTACCACCCACCCTTCCAGCGGCTAAAGCTACAGGCCT 1620
TTTCTTGCCATATTGCTGAGCTCAGGCAGTGAGGGCCCCACATTTGAGACAGTGAGCCCC 1680
AAGAAAAGGGTCCCTGGTGTACATCTCCAAGGTTGTCCAGGGTTGATCTCACAATGCGTT 1740
TCTTAAGCAGGTACACGTTTGCATGCCAATATGTGCTTCTGATCTGATTGGTTCATCCAA 1800
ACTACAACCCTGTCTCCCACCCATTCTCTCGGGAGTTTTGTTCCAGTGGGAATGACAAAT 1860
CACTTAGCAGATGGTCCTGAGCCCTCGGGCCAGCACTGCTGAGGAAGTGCCAGGGCCCCAG 1920
GCCAGGCTGCCAGAATTCCCCTTCGGGCTGGAGGATGAACAAAGCCCCTTGGGTTTTTCC 1980
ATCACCCCTGCACCCTATCTCACCATCAAACTGGCCCCCACATCAGTGAGAGGACACTTG 2040
ATGGAAAGCAATACACTTTAAGACTGAGCACACTTTCGTGCTCAGCTCTGTCTGGTCCTG 2100
TGACCTAGAGAAGCTCACCACATACATATAAAAATCAGAGGCTCATCTCCCTGTGGTTAG 2160
ACCCTACTCGCGGCGGTGTACTCCACCACAGCAGCACCGCACCGCTGGAAGTACAGTGCT 2220
GTCTTCAACACCTCTGAAAGAACCTGAGCTCACCGTGACAGTGCCCAGGGGAACCCTGCT 2280
TGCAGTCTATTGCATTTACATACCCCATTTCAGGGCACATTAGCATCCACTCCTATGGTA 2340
GCACACTGTTGACAATAGGACAACCCATAGGGGTTGACTATCCCTTATCCAAAATGCTTG 2400
GCACTAGAAGAGTTTTCGATTTTAGAGTCTTTTCAGGCATACGTATATTTGAGTATATAT 2460
AAAATGAGATATCTTGCCCGATGGGGCCCAACTATAAACATGAAGTTCATTTATATTTCAT 2520
AATACCGTATAGACACTCCTTGAAGTGTAGTTTTATACAGTGTTTTAAATAACGTTGTAT 2580
GCATGAAAGACGTTTTTACAGCATGAACCTCTCTACTCATGCCAGCACTCAAAAACCTTG 2640
GGGTTTTGGACCACTTTGGATCTTGGGTTTTCTGTTAAGAGATGGTTAGCTTATACCTAA 2700
AACCATAATCCCAAACAGGCTGCAGGACCAGACTGGATCCTCAGCCCTGAAGTGTGCCCT 2760
TCCAGCCAGGTCATACCCTGTCCAGGTGAGCGGGATCACCTTTTGTGGTGCTAAGAGACG 2820
ACTTGCAGGTAGATTTTCCACGATCTGAGGC                                2852
```

BEST AVAILABLE COPY

Figure 2

```
---G--GTTG CAAGGCCCAA GAAGCCCA-- -TCCTGGGAA GGAAAATGCA    50
TTGGGGAACC CTGTG-CGGA TTCTTGTGGC TTTGGCCCTA TCTTTTCTAT   100
GTCCAAGCTG TGCCCATCCA AAAAGTCCAA GATGACACCA AAACCCTCAT   150
CAAGACAATT GTCACCAGGA TCAATGACAT TTCACACACG CAGTCAGTCT   200
CCTCCAAACA GAAAGTCACC GGTTTGGACT TCATTCCTGG GCTCCACCCC   250
ATCCTGACCT TATCCAAGAT GGACCAGACA CTGGCAGTCT ACCAACAGAT   300
CCTCACCAGT ATGCCTTCCA GAAACGTGAT CCAAATATCC AACGACCTGG   350
AGAACCTCCG GGATCTTCTT CACGTGCTGG CCTTCTCTAA GAGCTGCCAC   400
TTGCCCTGGG CCAGTGGCCT GGAGACCTTG GACAGCCTGG GGGGTGTCCT   450
GGAAGCTTCA GGCTACTCCA CAGAGGTGGT GGCCCTGAGC AGGCTGCAGG   500
GGTCTCTGCA GGACATGCTG TGGCAGCTGG ACCTCAGCCC TGGGTGCTGA   550
GGCCTTGAAG GTCACTCTTC CTGCAAGGAC T-ACGTTAAG GGAAGGAACT   600
CTGGTTTCCA GGTATCTCCA GGATTGAAGA GCATTGCATG GACACCCCTT   650
ATCCAGGACT CTGTCAATTT CCCTGACTCC TCTAAGCCAC TCTTCCAAAG   700
G                                                        701
```

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Figure 3

1	Met His Trp Gly Thr Leu Cys Gly Phe Leu Trp Leu Trp Pro Tyr
16	Leu Phe Tyr Val Gln Ala Val Pro Ile Gln Lys Val Gln Asp Asp
31	Thr Lys Thr Leu Ile Lys Thr Ile Val Thr Arg Ile Asn Asp Ile
46	Ser His Thr Gln Ser Val Ser Ser Lys Gln Lys Val Thr Gly Leu
61	Asp Phe Ile Pro Gly Leu His Pro Ile Leu Thr Leu Ser Lys Met
76	Asp Gln Thr Leu Ala Val Tyr Gln Gln Ile Leu Thr Ser Met Pro
91	Ser Arg Asn Val Ile Gln Ile Ser Asn Asp Leu Glu Asn Leu Arg
106	Asp Leu Leu His Val Leu Ala Phe Ser Lys Ser Cys His Leu Pro
121	Trp Ala Ser Gly Leu Glu Thr Leu Asp Ser Leu Gly Gly Val Leu
136	Glu Ala Ser Gly Tyr Ser Thr Glu Val Val Ala Leu Ser Arg Leu
151	Gln Gly Ser Leu Gln Asp Met Leu Trp Gln Leu Asp Leu Ser Pro
166	Gly Cys End

Figure 4

```
Mouse   MCWRPLCRFL WLWSYLSYVQ AVPIQKVQDD TKTLIKTIVT RINDISHTQS    50
         * **  *      *  *
Human   MHWGTLCGFL WLWPYLFYVQ AVPIQKVQDD TKTLIKTIVT RINDISHTQS

Mouse   VSAKQRVTGL DFIPGLHPIL SLSKMDQTLA VYQQVLTSLP SQNVLQIAND    100
          *                   -              -   -   *     *
Human   VSSKQKVTGL DFIPGLHPIL TLSKMDQTLA VYQQILTSMP SRNVIQISND

Mouse   LENLRDLLHL LAFSKSCSLP QTSGLQKPES LDGVLEASLY STEVVALSRL    150
                 -        *   **   ***-   *      *
Human   LENLRDLLHV LAFSKSCHLP WASGLETLDS LGGVLEASGY STEVVALSRL

Mouse   QGSLQDILQQ LDVSPEC                                        167
              - *    -  *
Human   QGSLQDMLWQ LDLSPGC
```

Figure 5

1	Met Cys Trp Arg Pro Leu Cys Arg Phe Leu Trp Leu Trp Ser Tyr
16	Leu Ser Tyr Val Gln Ala Val Pro Ile Gln Lys Val Gln Asp Asp
31	Thr Lys Thr Leu Ile Lys Thr Ile Val Thr Arg Ile Asn Asp Ile
46	Ser His Thr Ser Val Ser Ala Lys Gln Arg Val Thr Gly Leu Asp
61	Phe Ile Pro Gly Leu His Pro Ile Leu Ser Leu Ser Lys Met Asp
76	Gln Thr Leu Ala Val Tyr Gln Gln Val Leu Thr Ser Leu Pro Ser
91	Gln Asn Val Leu Gln Ile Ala Asn Asp Leu Glu Asn Leu Arg Asp
106	Leu Leu His Leu Leu Ala Phe Ser Lys Ser Cys Ser Leu Pro Gln
121	Thr Ser Gly Leu Gln Lys Pro Glu Ser Leu Asp Gly Val Leu Glu
136	Ala Ser Leu Tyr Ser Thr Glu Val Val Ala Leu Ser Arg Leu Gln
151	Gly Ser Leu Gln Asp Ile Leu Gln Gln Leu Asp Val Ser Pro Glu
166	Cys End

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Figure 6

1	Met	His	Trp	Gly	Thr	Leu	Cys	Gly	Phe	Leu	Trp	Leu	Trp	Pro	Tyr
16	Leu	Phe	Tyr	Val	Gln	Ala	Val	Pro	Ile	Gln	Lys	Val	Gln	Asp	Asp
31	Thr	Lys	Thr	Leu	Ile	Lys	Thr	Ile	Val	Thr	Arg	Ile	Asn	Asp	Ile
46	Ser	His	Thr	Ser	Val	Ser	Ser	Lys	Gln	Lys	Val	Thr	Gly	Leu	Asp
61	Phe	Ile	Pro	Gly	Leu	His	Pro	Ile	Leu	Thr	Leu	Ser	Lys	Met	Asp
76	Gln	Thr	Leu	Ala	Val	Tyr	Gln	Gln	Ile	Leu	Thr	Ser	Met	Pro	Ser
91	Arg	Asn	Val	Ile	Gln	Ile	Ser	Asn	Asp	Leu	Glu	Asn	Leu	Arg	Asp
106	Leu	Leu	His	Val	Leu	Ala	Phe	Ser	Lys	Ser	Cys	His	Leu	Pro	Trp
121	Ala	Ser	Gly	Leu	Glu	Thr	Leu	Asp	Ser	Leu	Gly	Gly	Val	Leu	Glu
136	Ala	Ser	Gly	Tyr	Ser	Thr	Glu	Val	Val	Ala	Leu	Ser	Arg	Leu	Gln
151	Gly	Ser	Leu	Gln	Asp	Met	Leu	Trp	Gln	Leu	Asp	Leu	Ser	Pro	Gly
166	Cys	End													

Figure 7

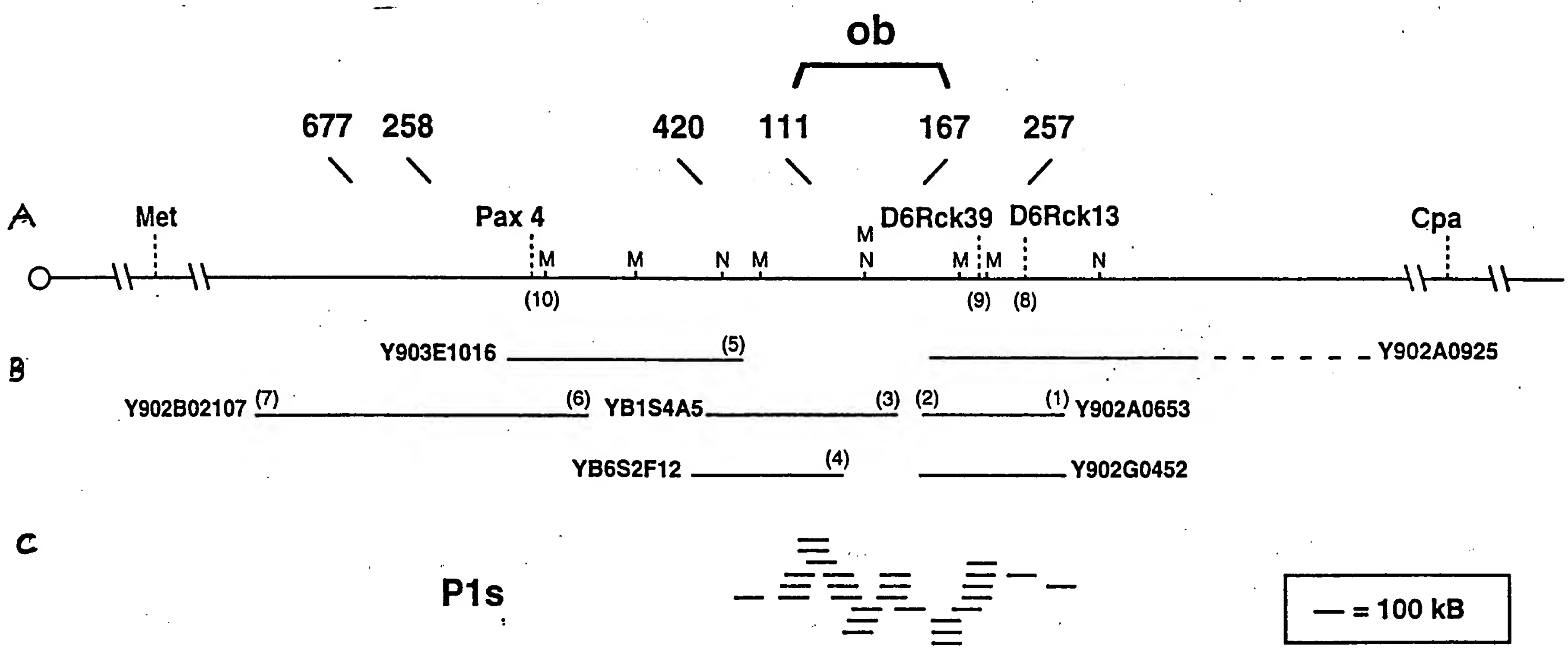

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Figure 8

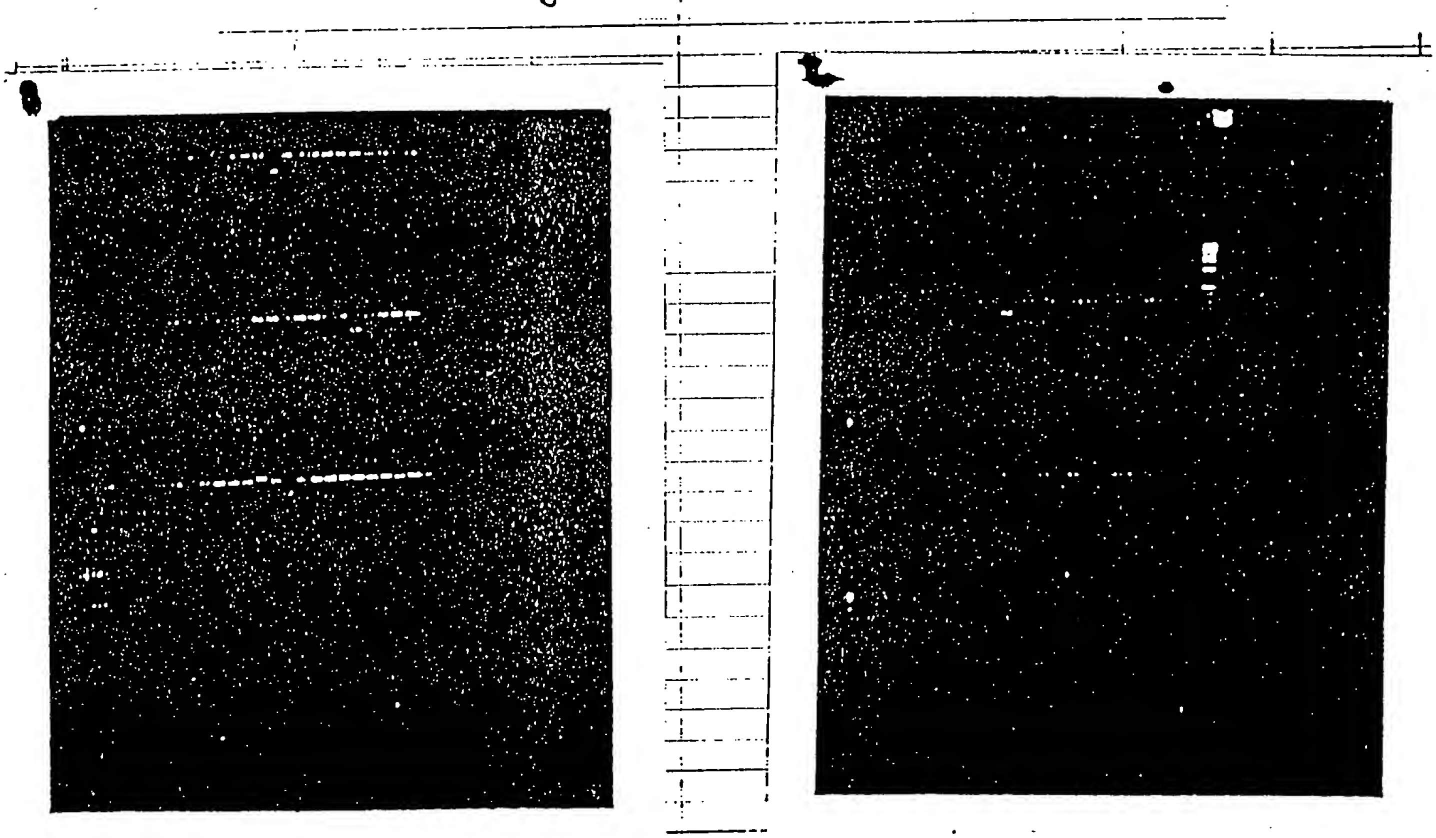

Figure 9

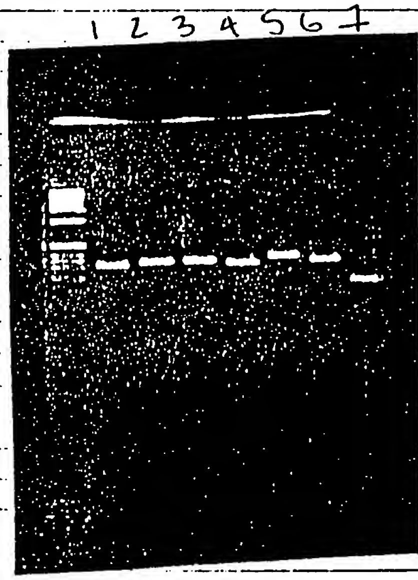

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Figure 10

```
          +10        +20        +30        +40
    GTGCAAGAAG AAGAAGATCC CAGGGCAGGA AAATGTGCTG GAGACCCCTG
1   ---------- ---------- ---------- ---------- ----------
    CACGTTCTTC TTCTTCTAGG GTCCCGTCCT TTTACACGAC CTCTGGGGAC
          +10        +20        +30        +40
    TGTCGGGTCC NGTGGNTTTG GTCCTATCTG TCTTATGTNC AAGCAGTGCC
51  ---------- ?----?---- ---------- --------?- ----------
    ACAGCCCAGG NCACCNAAAC CAGGATAGAC AGAATACANG TTCGTCACGG
          +10        +20     ?  +30       ? +40
    TATCCAGAAA GTCCAGGATG ACACCAAAAG CCTCATCAAG ACCATTGTCA
101 ---------- ---------- ---------- ---------- ----------
    ATAGGTCTTT CAGGTCCTAC TGTGGTTTTC GGAGTAGTTC TGGTAACAGT
          +10        +20        +30        +40
    NCAGGATCAC TGANATTTCA CACACG
151 ?--------- ---?------ ------
    NGTCCTAGTG ACTNTAAAGT GTGTGC
```

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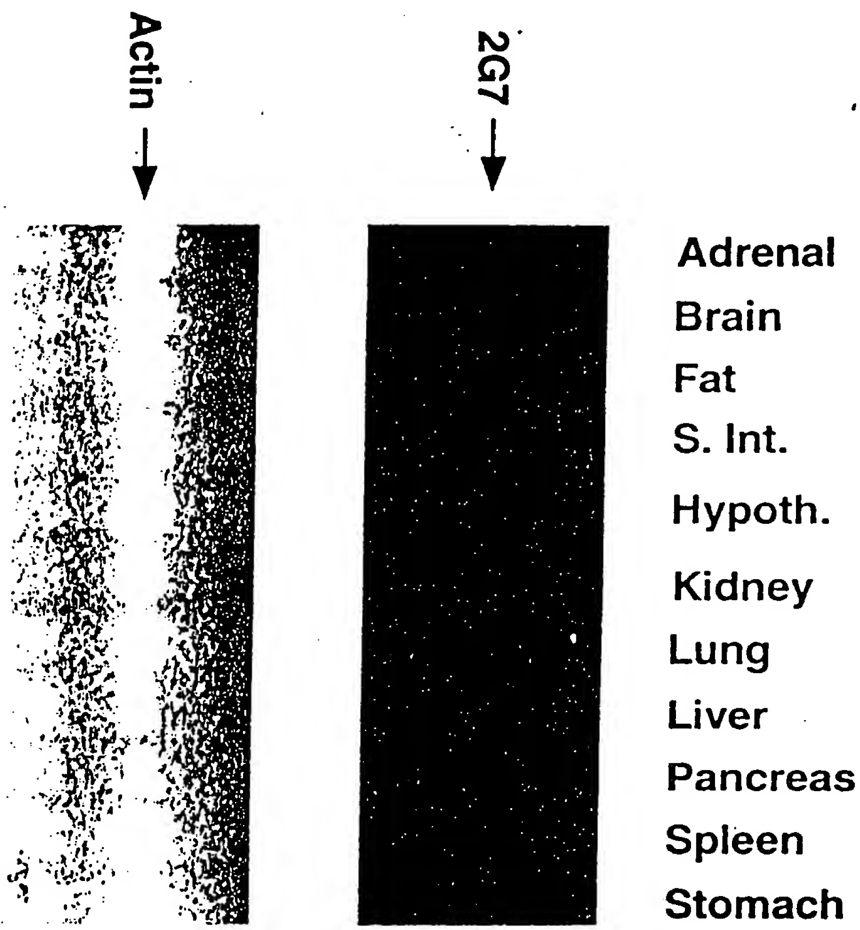
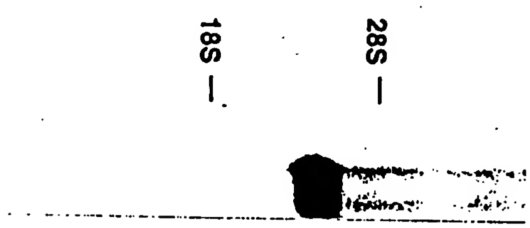
Figure 11A



08/485943

Figure 11B



white fat
brain
small intestine
stomach
pancreas
lung
testis
heart
spleen
liver

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Figure 12A

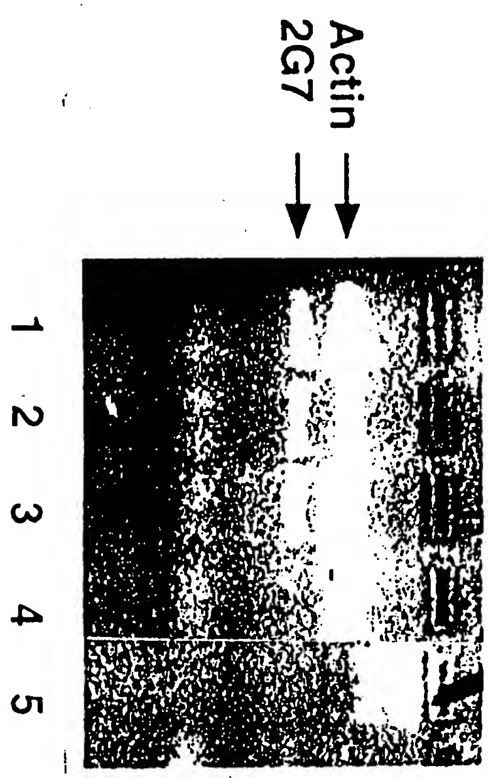
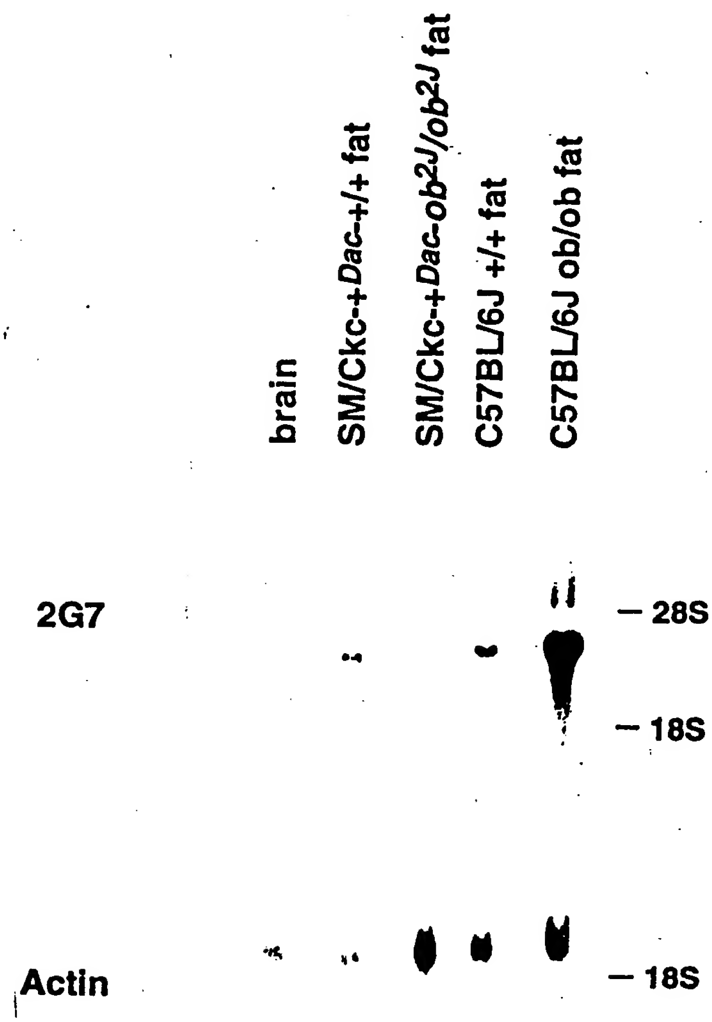


Figure 12 B


brain
SM/Ckc-+Dac-+/+ fat
SM/Ckc-+Dac-ob2J/ob2J fat
C57BL/6J +/+ fat
C57BL/6J ob/ob fat
2G7
28S
18S
Actin
18S

08/485943

Figure 13

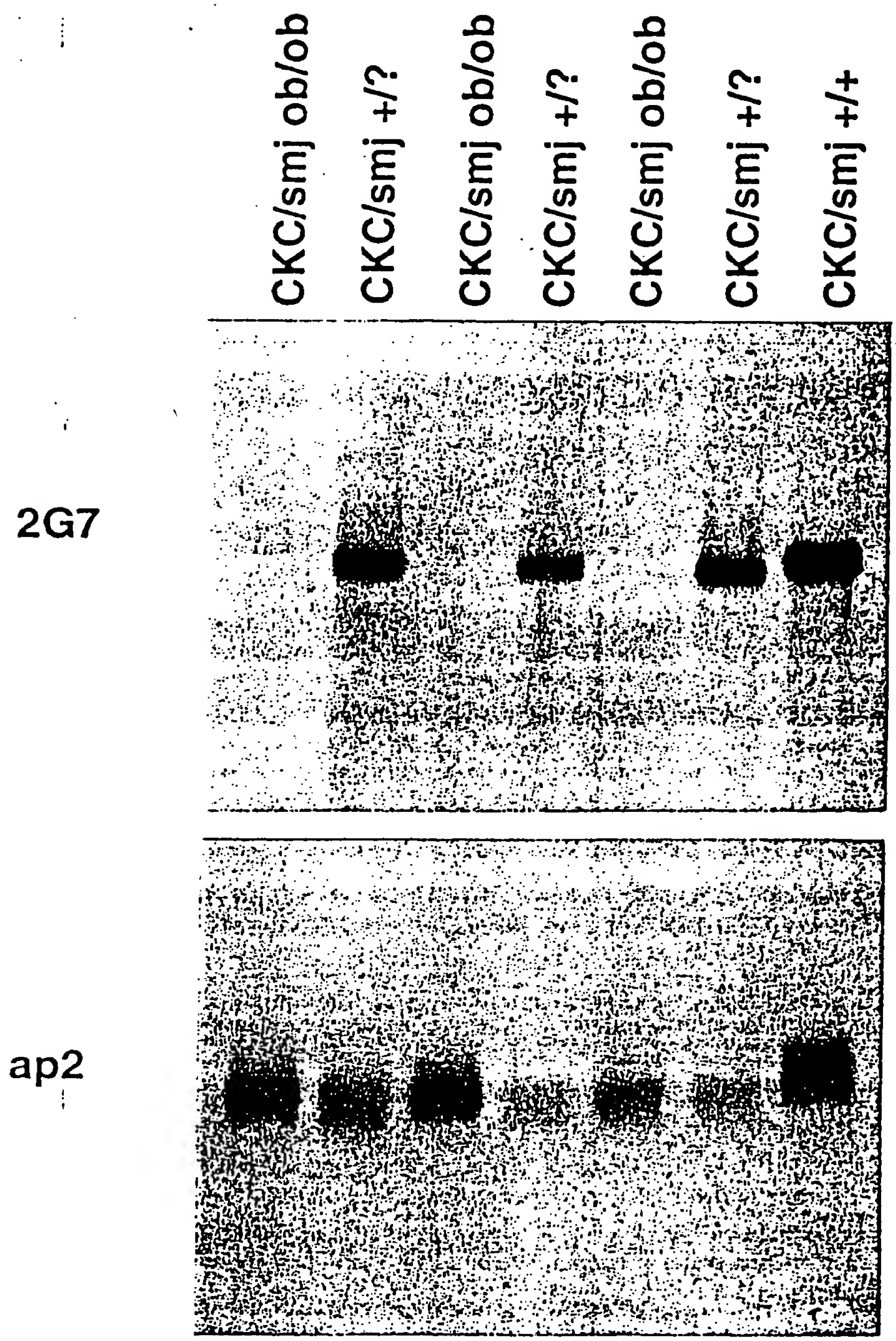


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Figure 14

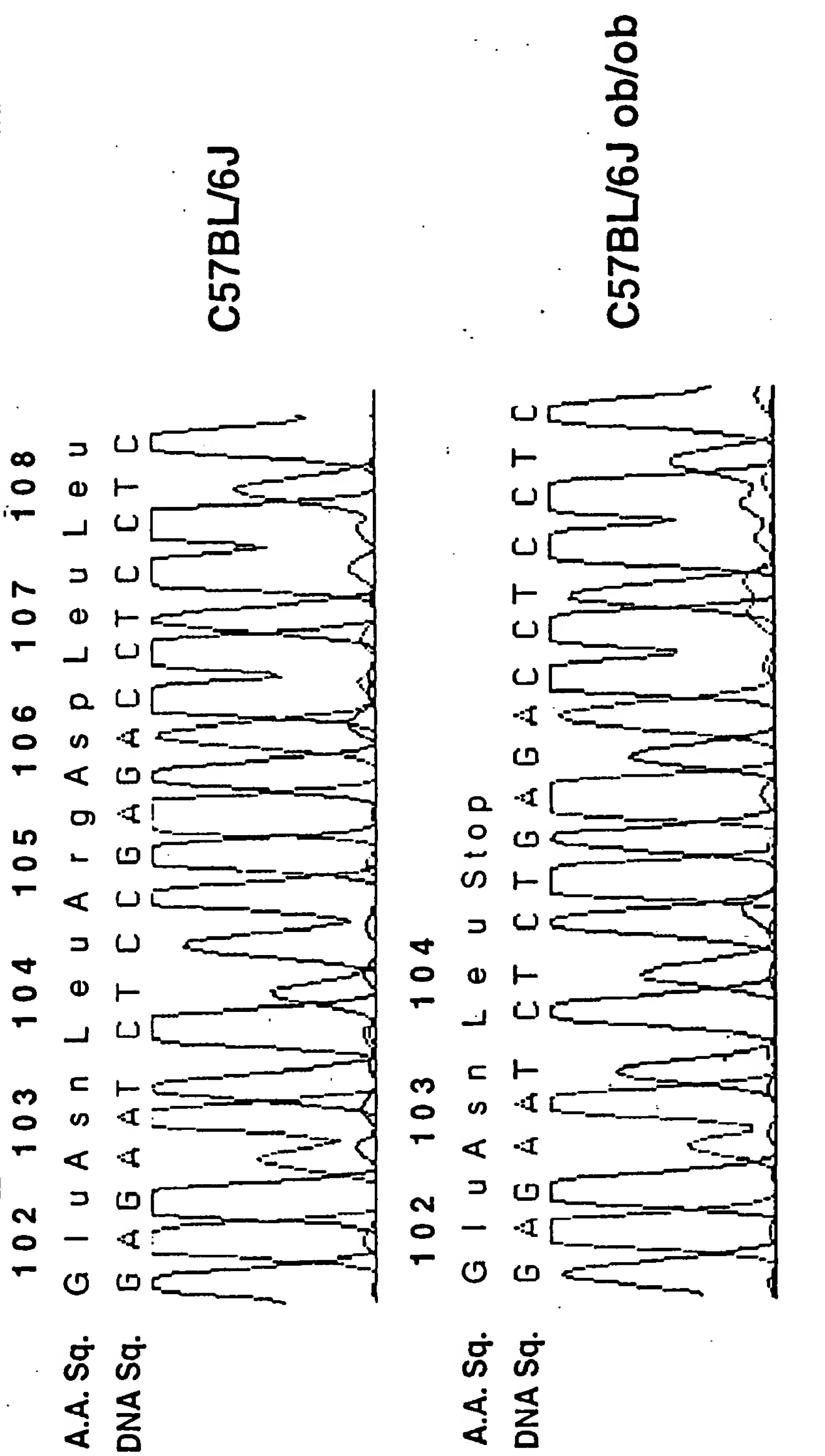

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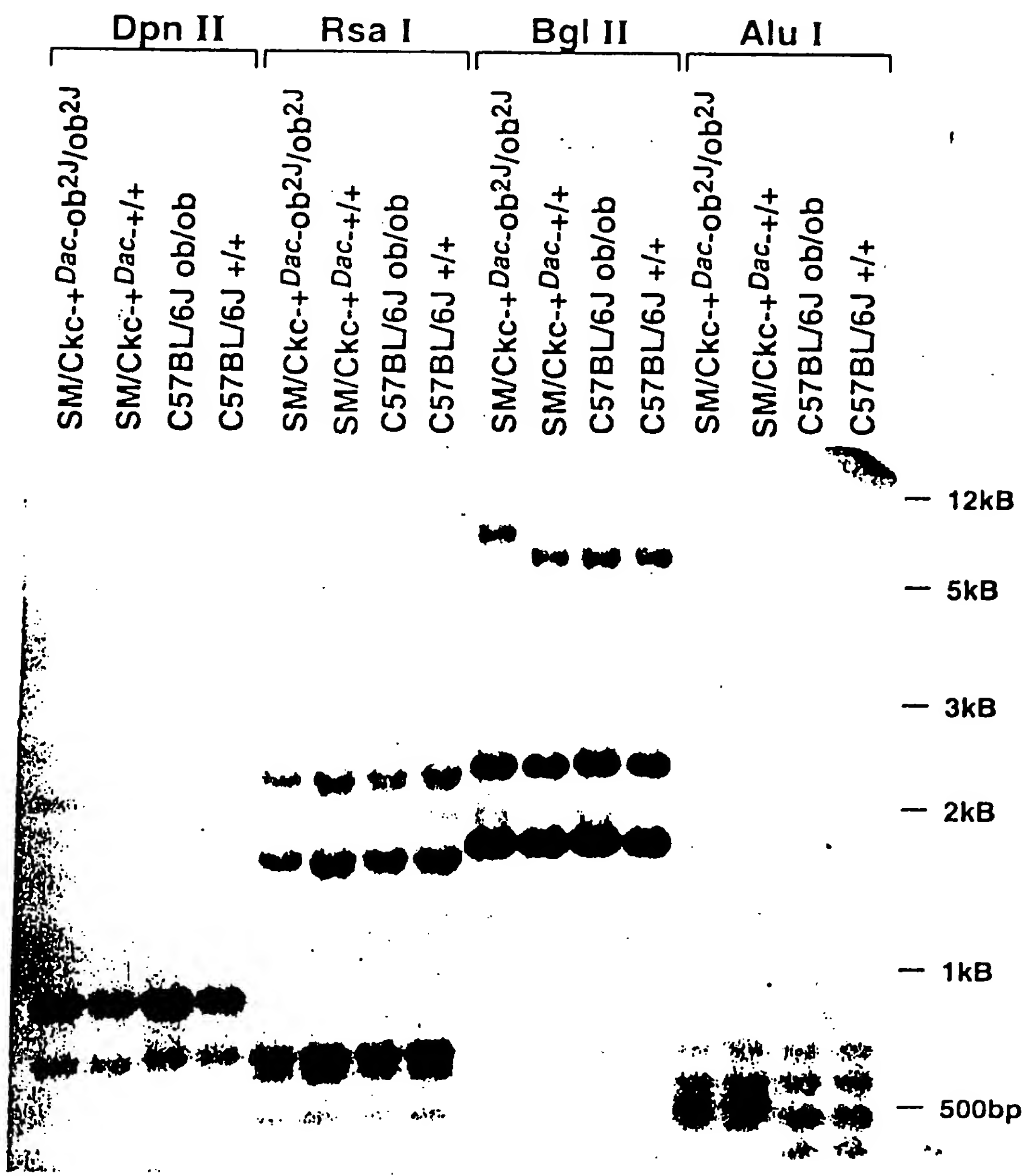
Figure 15A



600-1-087 CIP2 (Sheet 10 of 24)

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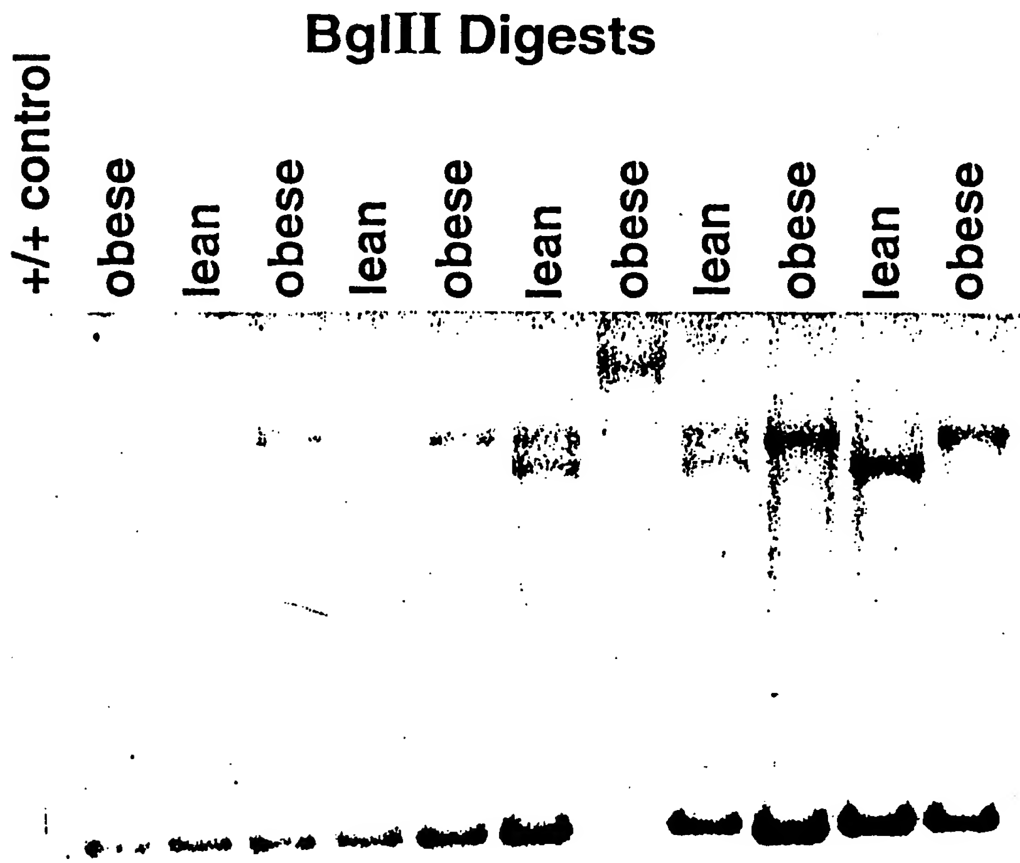
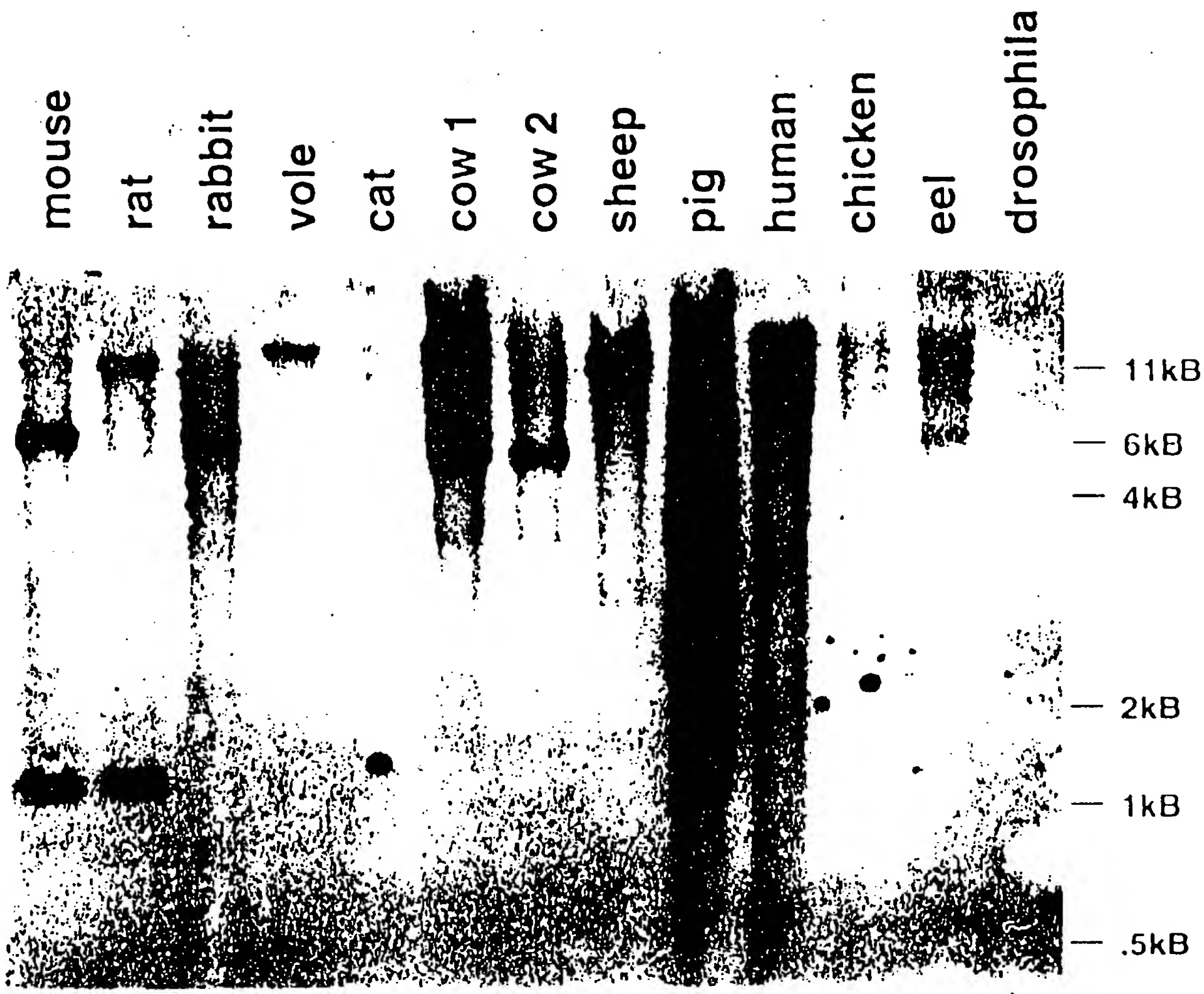
Figure 15B



08/485943

Figure 16



08/485943

Figure 17

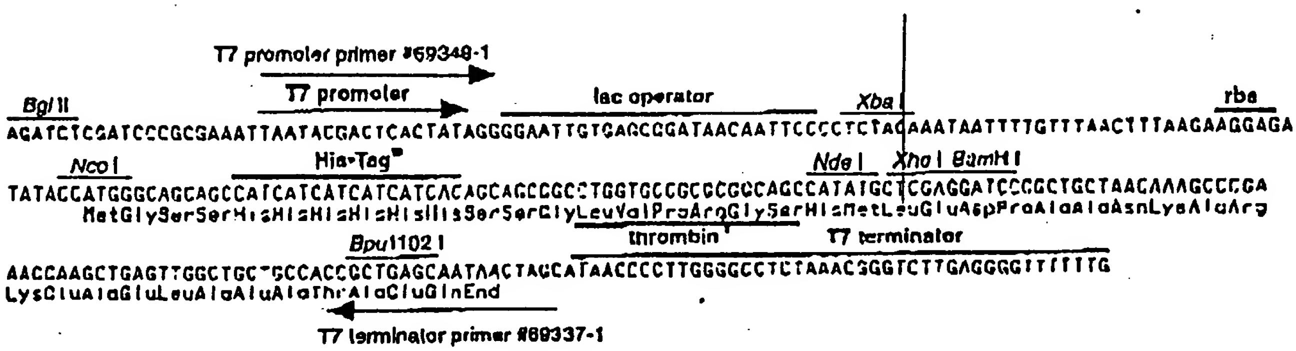


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Figure 18A

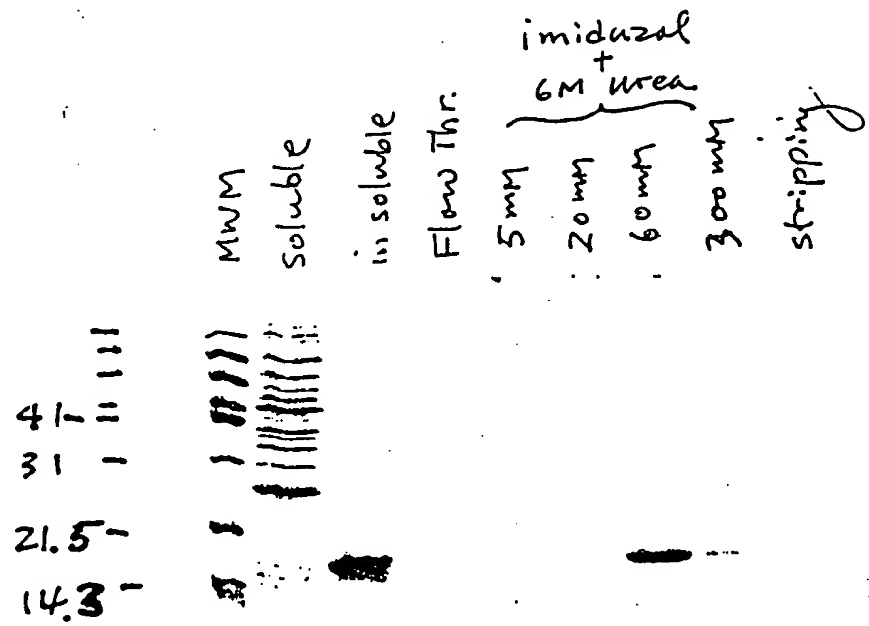

Figure 18B

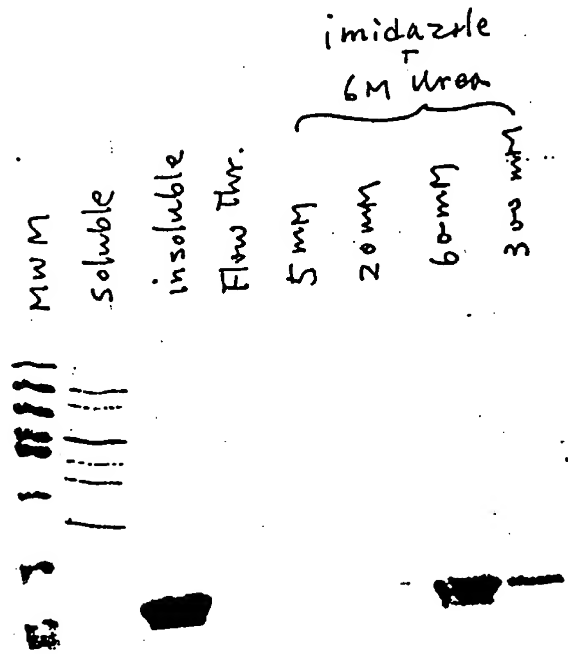
imidazole
+
6M urea
MWM
soluble
insoluble
Flow thr.
5 mM
20 mM
60 mM
300 mM

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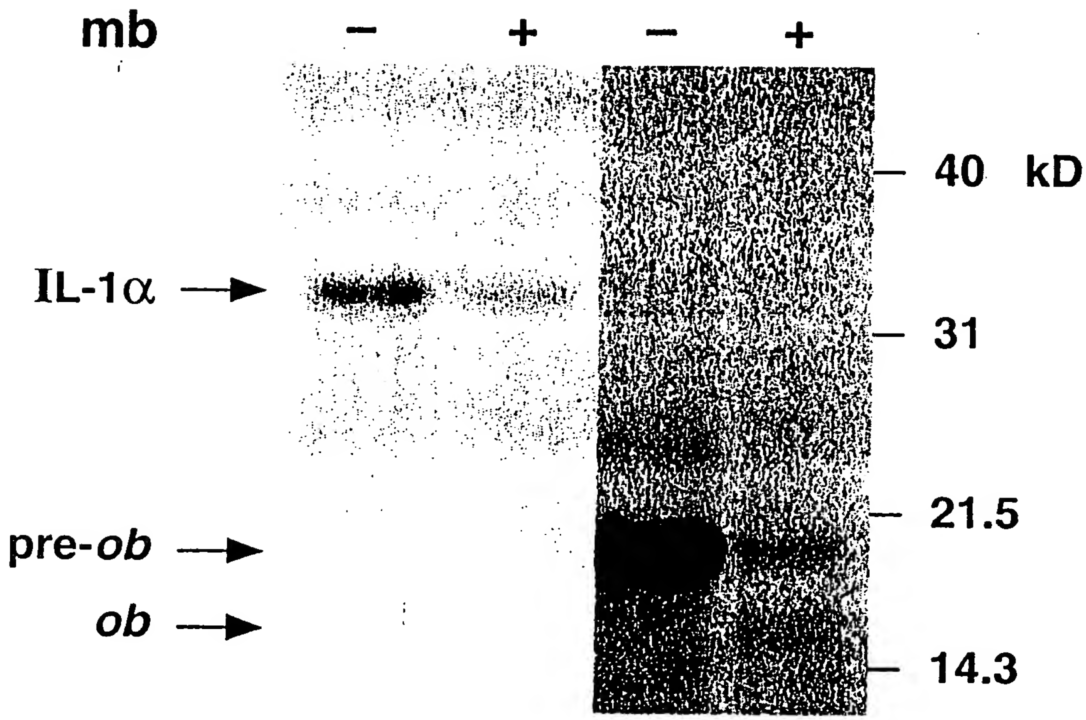
Figure 19A



08/485943

Figure 19B

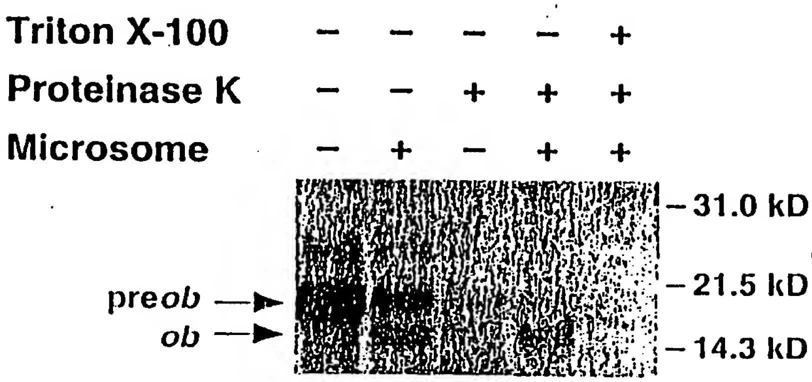


Figure 20A

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```
        10         20         30         40         50
GGTTGCAAGG CCCAAGAAGC CCATCCTGGG AAGGAAAATG CATTGGGGAA
           HOB1gF                      START
        60         70         80         90        100
CCCTGTGCGG ATTCTTGTGG CTTTGGCCCT ATCTTTTCTA TGTCCAAGCT
       110        120        130        140        150
GTGCCCATCC AAAAAGTCCA AGATGACACC AAAACCCTCA TCAAGACAAT
                                 5' of 1st INTRON
       160        170        180        190        200
TGTCACCAGG ATCAATGACA TTTCACACAC GGTAAGGAGA GTATGCGGGG
       210        220        230        240        250
ACAAAGTAGA ACTGCAGCCA GCCCAGCACT GGCTCCTAGT GGCACTGGAC
                                              HOB1g R
       260        270        280        290        300
CCAGATAGTC CAAGAAACAT TTATTGAACG CCTCCTGAAT GCCAGGCACC
       310        320        330        340        350
TACTGCAAGC TGAGAAGGAT TTTGGATAGC ACAGGCCTCC ACTCTTTCTG
       360        370        380        390        400
GTTGTTTCTT NTGGCCCCCT CTGCCTGCTG AGATNCCAGG GGTTAGNGGT
       410        420        430        440        450
TCTTAATTCC TAAA---- GAP OF SEQUENCE (~1.4 kb) ----CT
       460        470        480        490        500
GGTTCTTTCA GGAAGAGGCC ATGTAAGAGA AAGGAATTGA CCTAGGGAAA
       510        520        530        540        550
ATTGGCCTGG GAAGTGGAGG GAACGGATGG TGTGGGAAAA GCAGGAATCT
       560        570        580        590        600
CGGAGACCAG CTTAGAGGCT TGGCAGTCAC CTGGGTGCAG GANACAAGGG
       610        620        630        640        650
CCTGAGCCAA AGTGGTGAGG GAGGGTGGAA GGAGACAGCC CAGAGAATGA
       660        670        680        690        700
CCCTCCATGC CCACGGGGAA GGCAGAGGGC TCTGAGAGCG ATTCCTCCCA
                     3' of 1st INTRON
       710        720        730        740        750
CATGCTGAGC ACTTGTTCTC CCTCTTCCTC CTNCATAGCA GTCAGTCTCC
HOB2gF
       760        770        780        790        800
TCCAAACAGA AAGTCACCGG TTTGGACTTC ATTCCTGGGC TCCACCCCAT
       810        820        830        840        850
CCTGACCTTA TCCAAGATGG ACCAGACACT GGCAGTCTAC CAACAGATCC
       860        870        880        890        900
TCACCAGTAT GCCTTCCAGA AACGTGATCC AAATATCCAA CGACCTGGAG
```

```
       910        920        930        940        950
AACCTCCGGG ATCTTCTTCA CGTGCTGGCC TTCTCTAAGA GCTGCCACTT
       960        970        980        990       1000
GCCCTGGGcC AGTGGCCTGG AGACCTTGGA CAGCCTGGGG GGTGTCCTGG
      1010       1020       1030       1040       1050
AAGCTTCAGG CTACTCCACA GAGGTGGTGG CCCTGAGCAG GCTGCAGGGG
      1060       1070       1080       1090       1100
TCTCTGCAGG ACATGCTGTG GCAGCTGGAC CTCAGCCCTG GGTGCTGAGG
                                                STOP
      1110       1120       1130       1140       1150
CCTTGAAGGT CACTCTTCCT GCAAGGACTA CGTTAAGGGA AGGAACTCTG
      1160       1170       1180       1190       1200
GcTTCCAGGT ATCTCCAGGA TTGAAGAGCA TTGCATGGAC ACCCCTTATC
                 HOB2g R
      1210       1220       1230       1240       1250
CAGGACTCTG TCAATTTCCC TGACTCCTCT AAGCCACTCT TCCAAAGG
```

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Figure 20B

MOUSE OB STRUCTURE

!st ex   lst intr   2nd ex   2nd intr   3rd exon

______//////////____ATG_______________////////////________________________TGA______

start   stop

Figure 20c

HUMAN OB STUCTURE

1st exon   1st lntr   2nd exon

....................____ATG_______________///////////_______________________________TGA______

start   stop

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Figure 21A

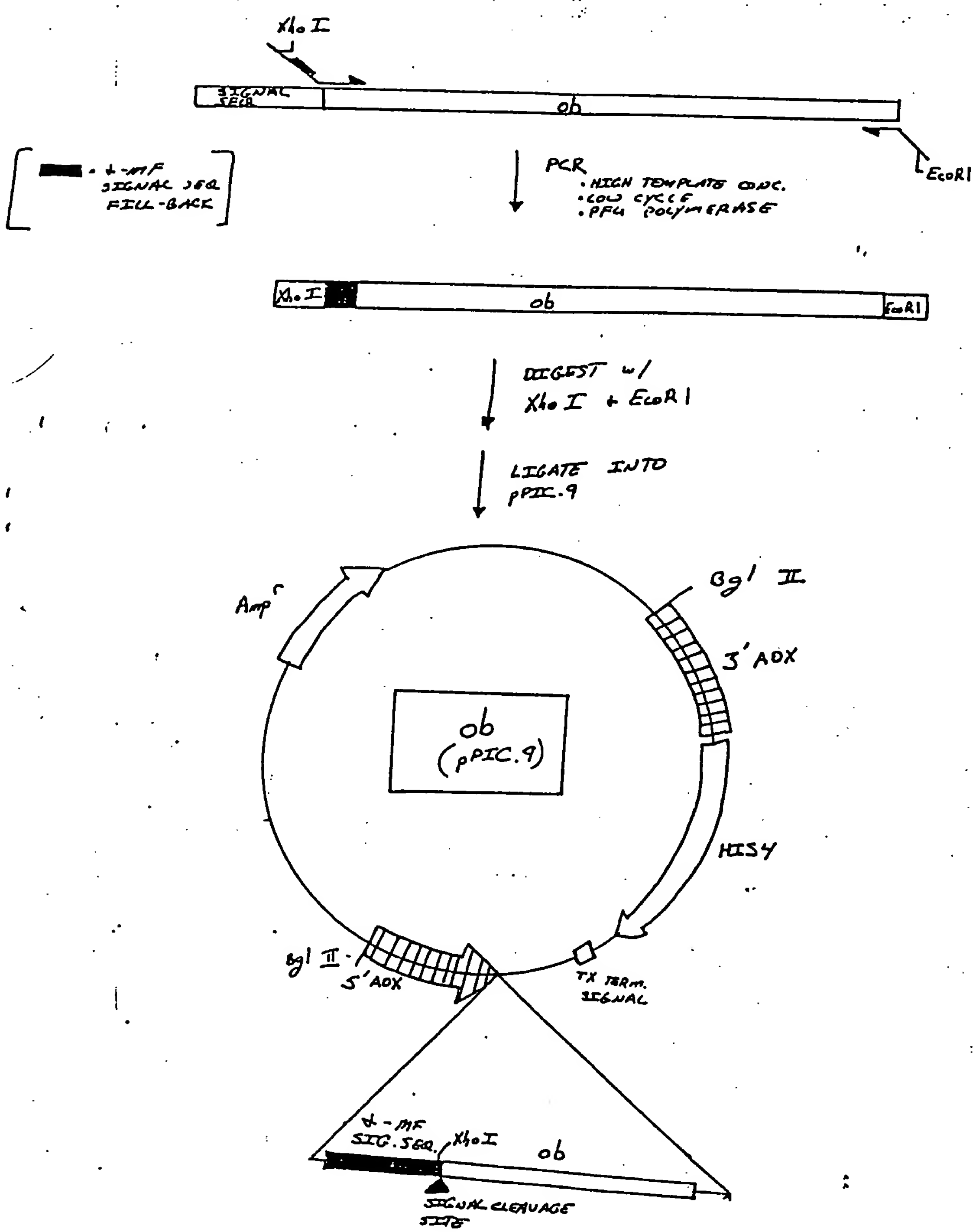

Figure 21 B

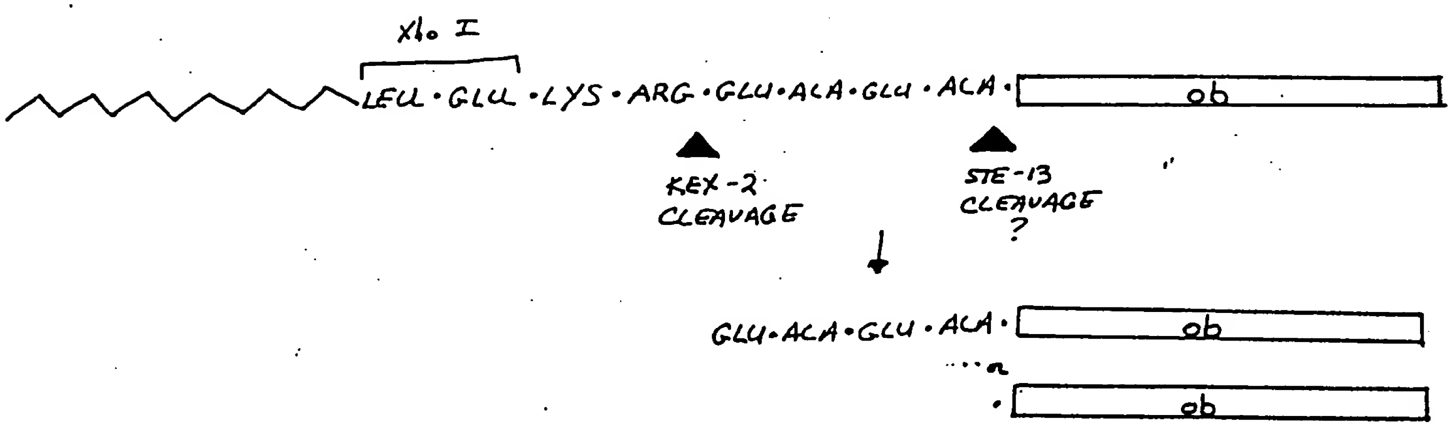

Figure 21 C

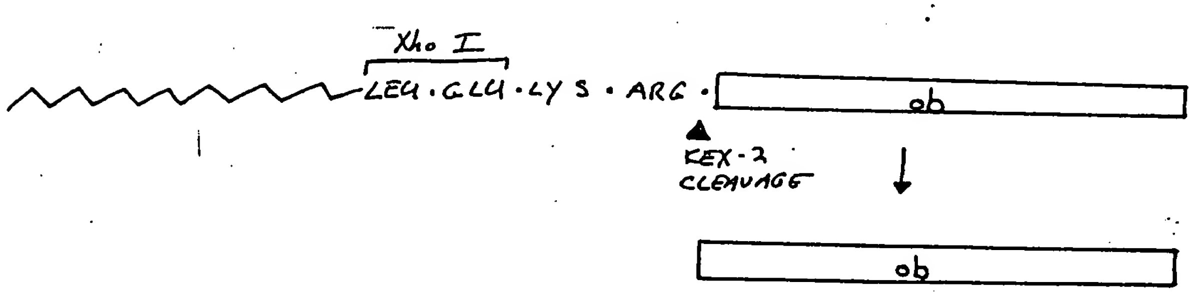

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Figure 22A

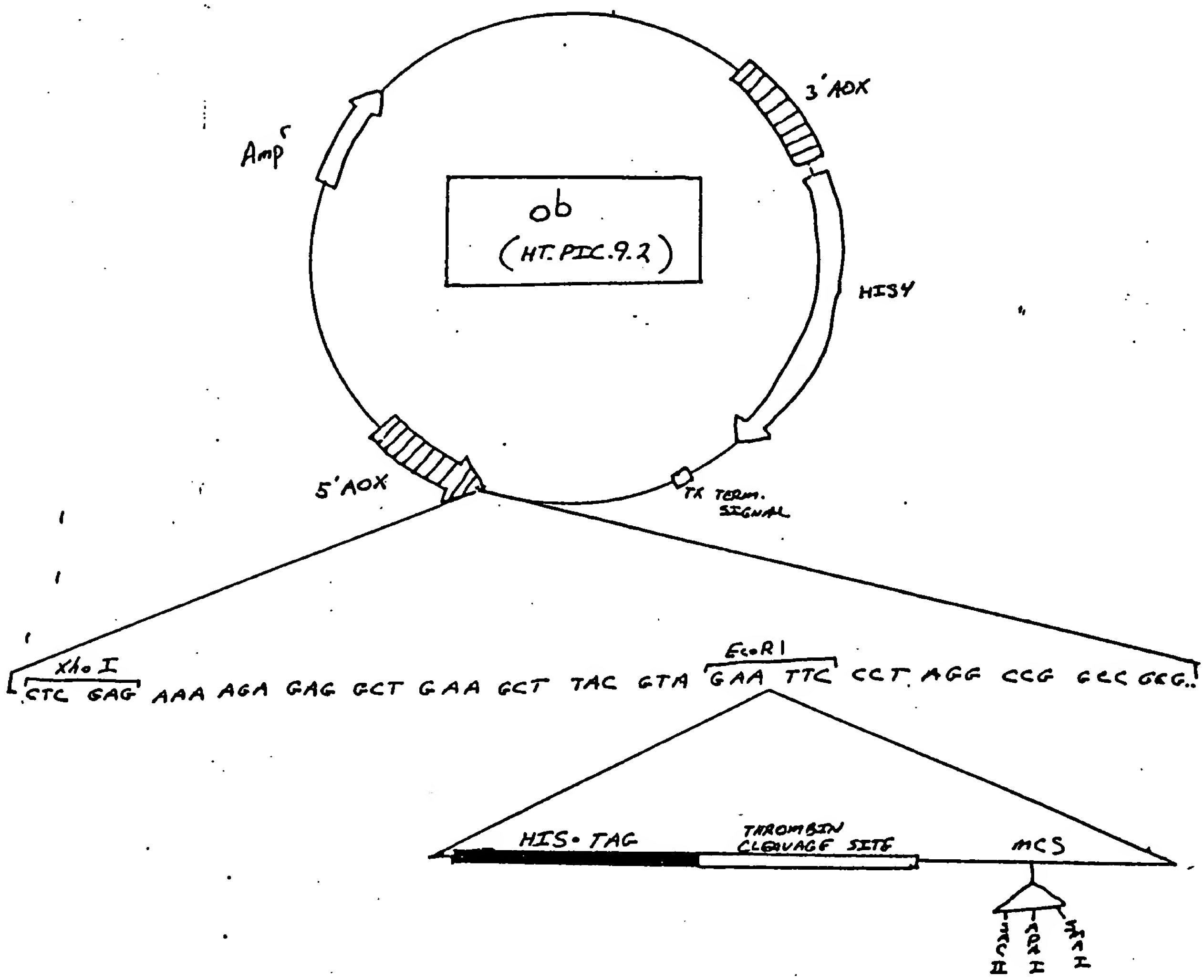


Figure 22B

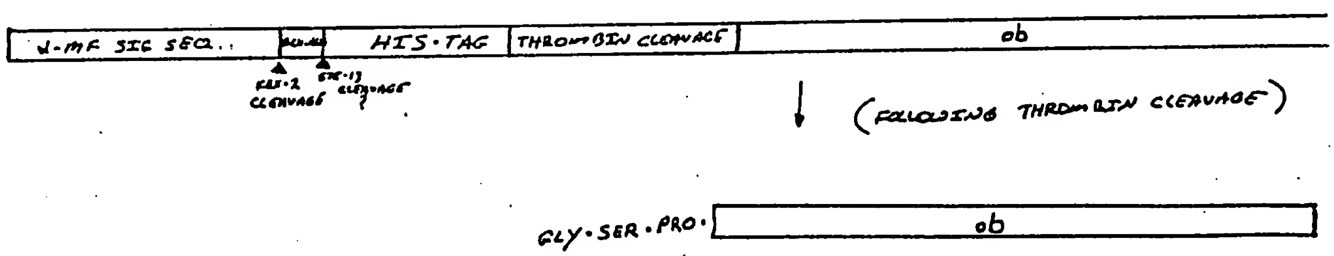

α-MF SIG SEQ.
HIS·TAG
THROMBIN CLEAVAGE
ob
KEX-2 CLEAVAGE
STE-13 CLEAVAGE ?
(FOLLOWING THROMBIN CLEAVAGE)
GLY·SER·PRO·
ob

Figure 23A

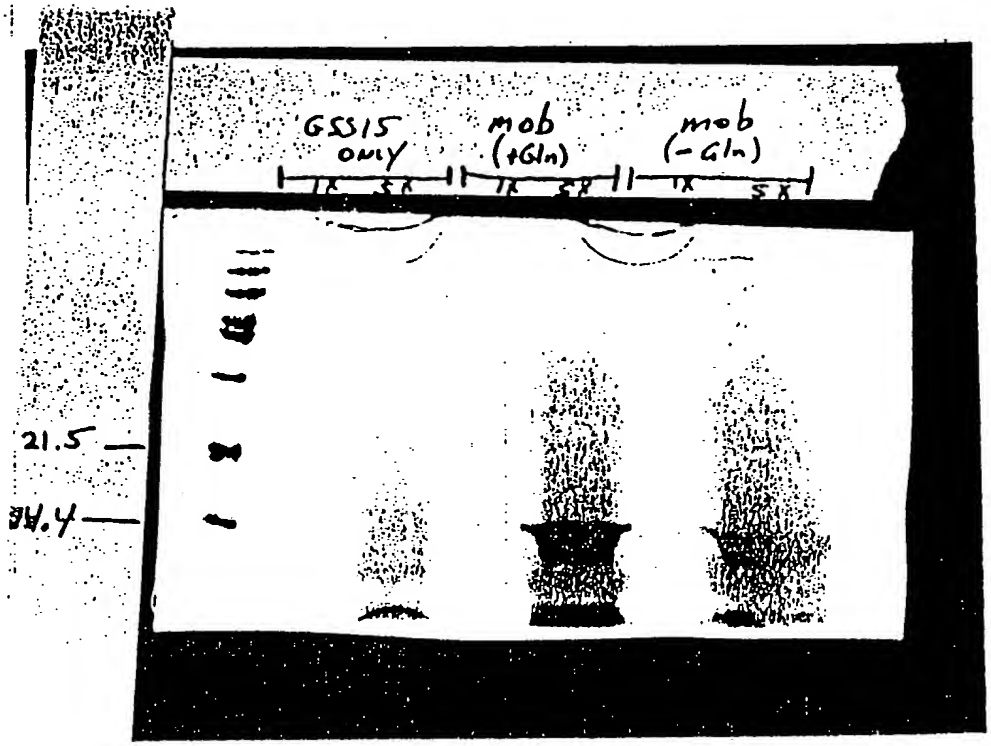


Figure 23B

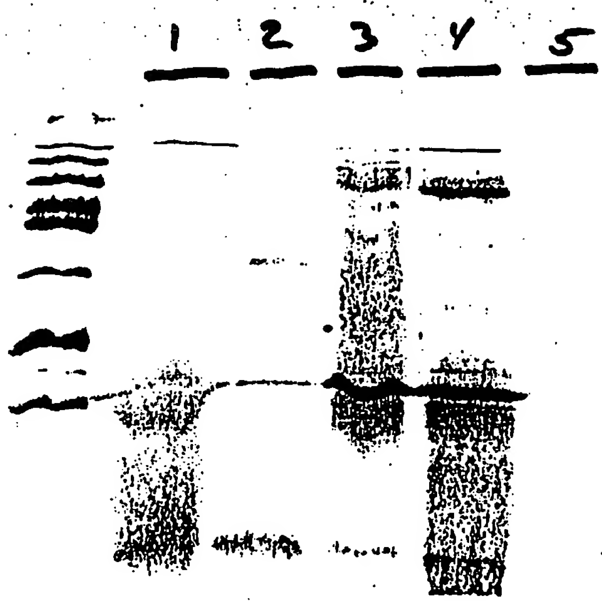
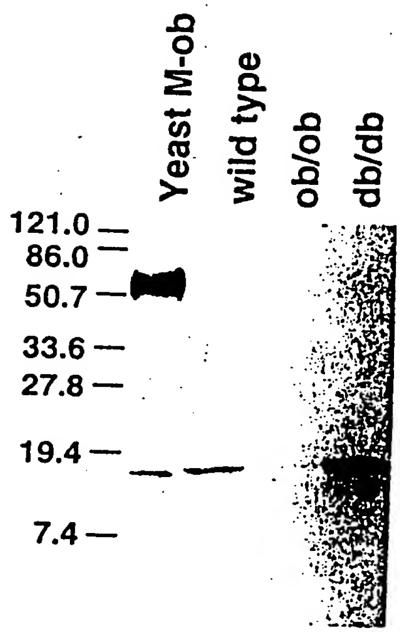
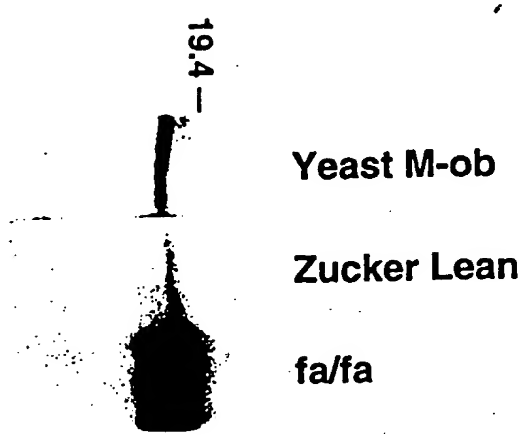


Figure 24 A



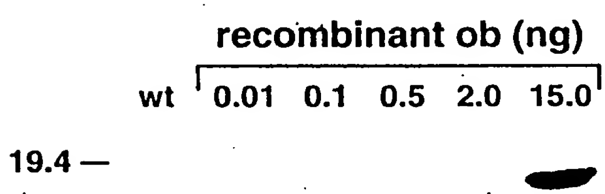
08/485943

Figure 24B



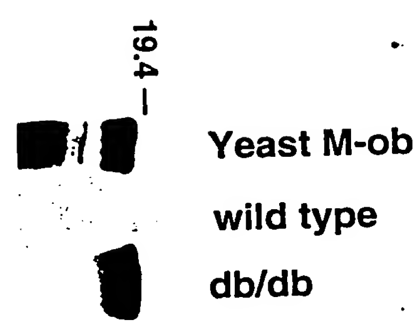
08/485943

Figure 24C



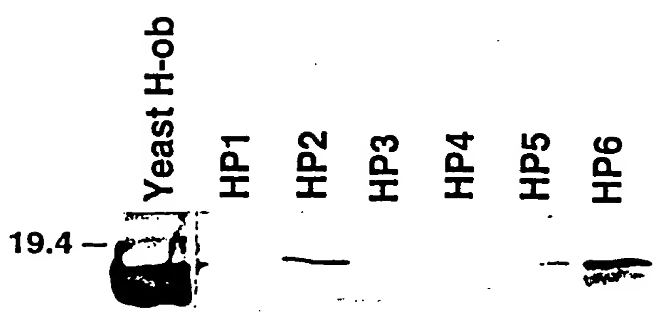
08/485943

Figure 24 D



08/485943

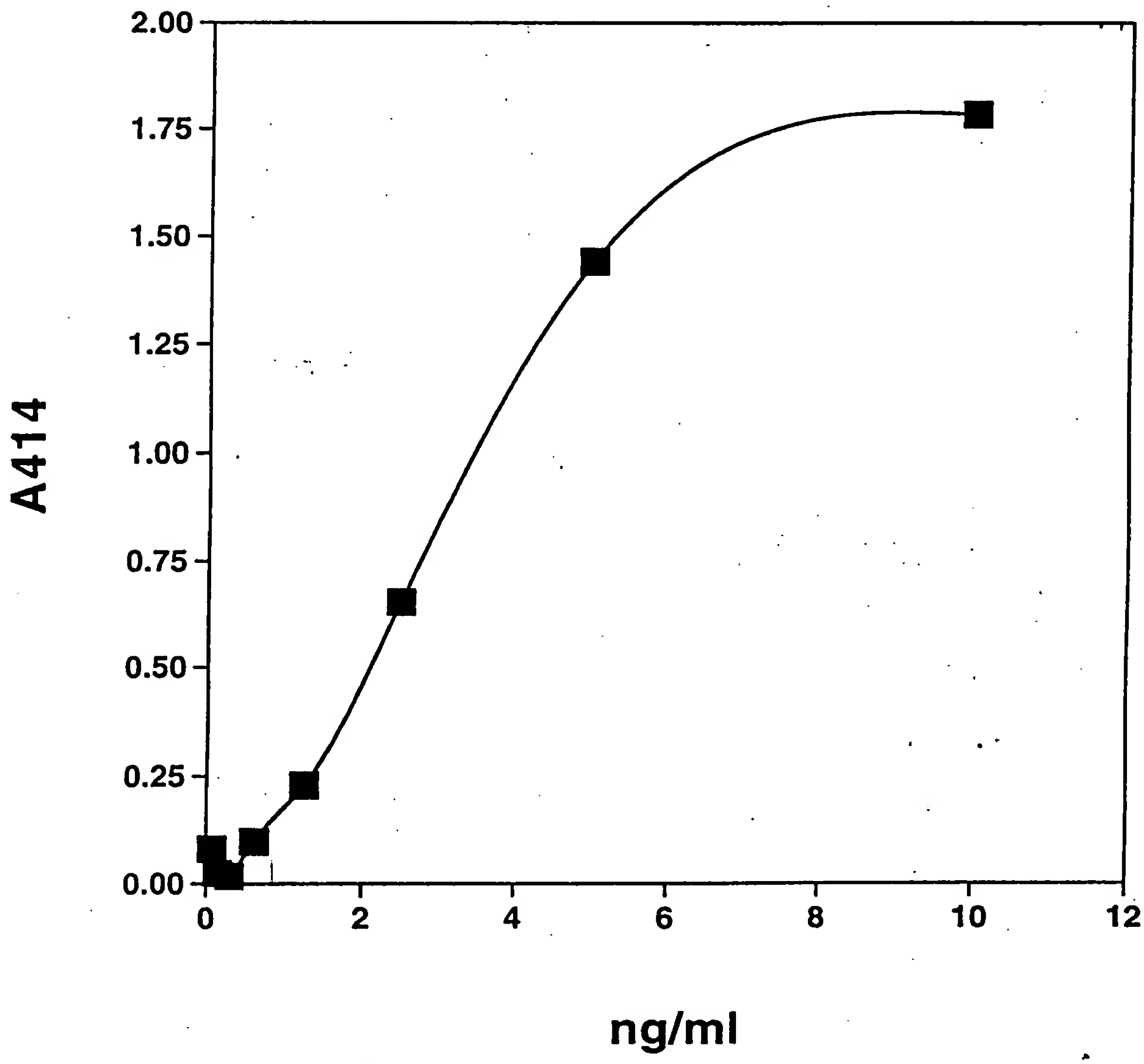
Figure 25A



08/485943

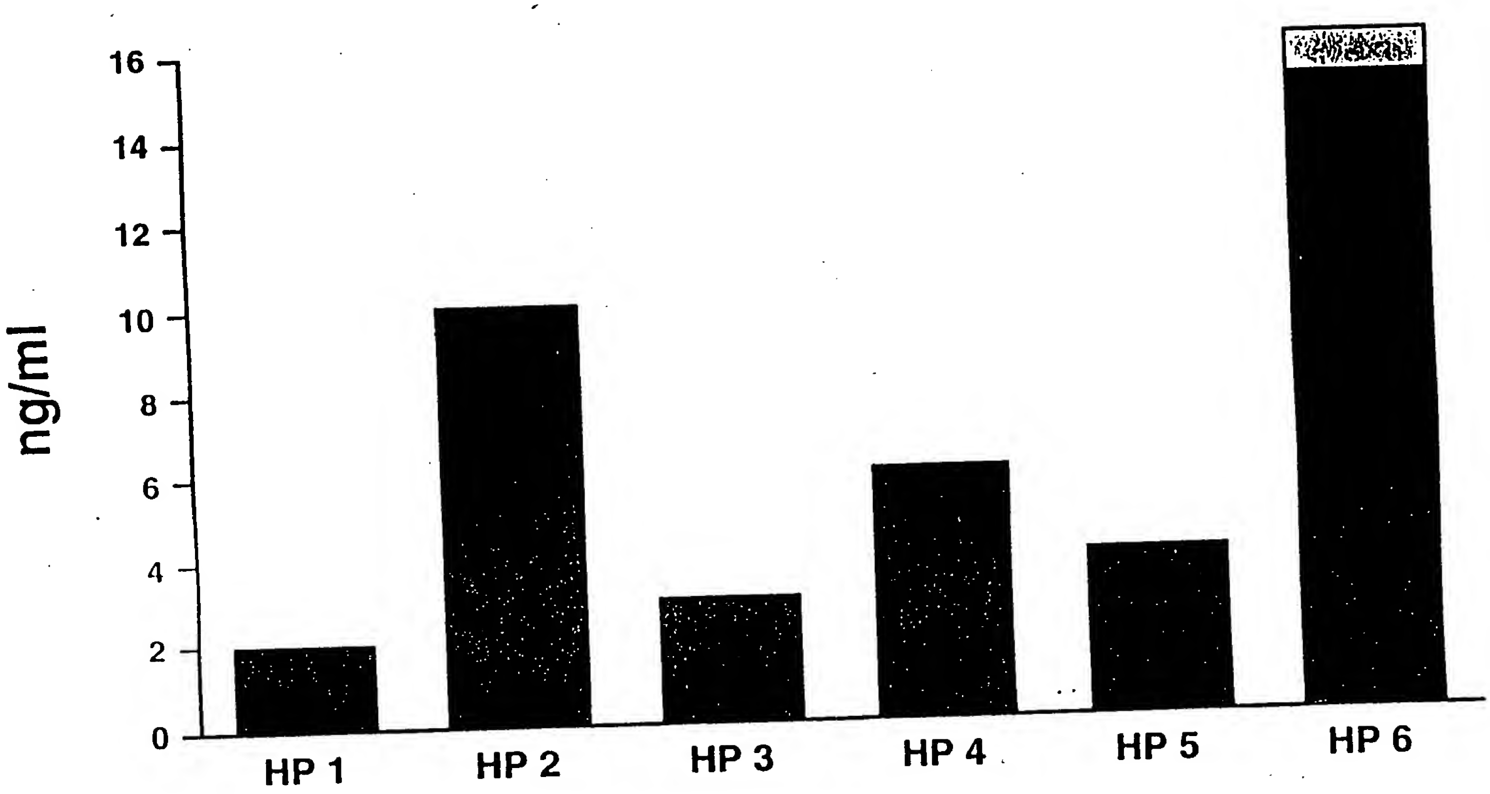
Figure 25 B

ELISA STANDARD CURVE



08/485943

Figure 25C



08/485943

Figure 26A

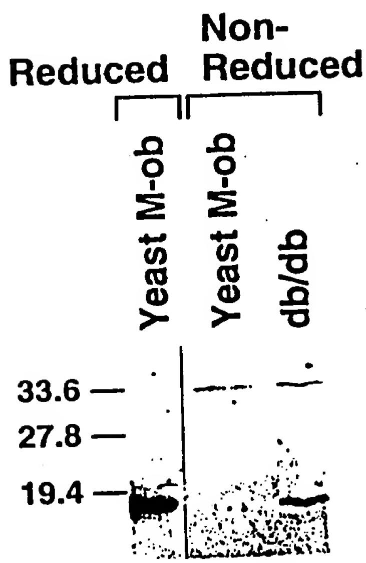


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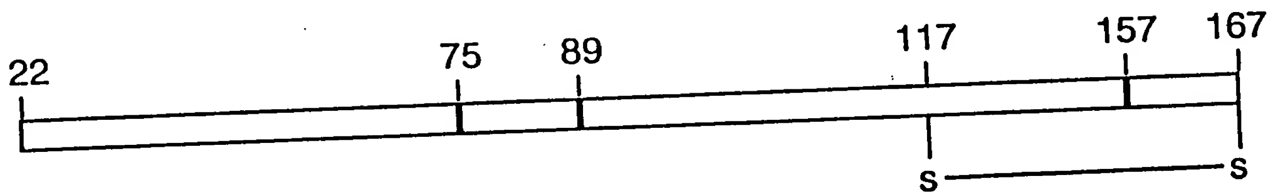
Figure 26 B

Human ob



Peptide	Mass(Da) Expected	Mass(Da) Observed
22-167	16,024	16,024 ± 3
22-75	5936.9	5936.6 ± 1
76-89	1562.7	N.D.
90-167	8434.5	8435.6 ± 1
158-167	1131.9	N.D.

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Figure 27

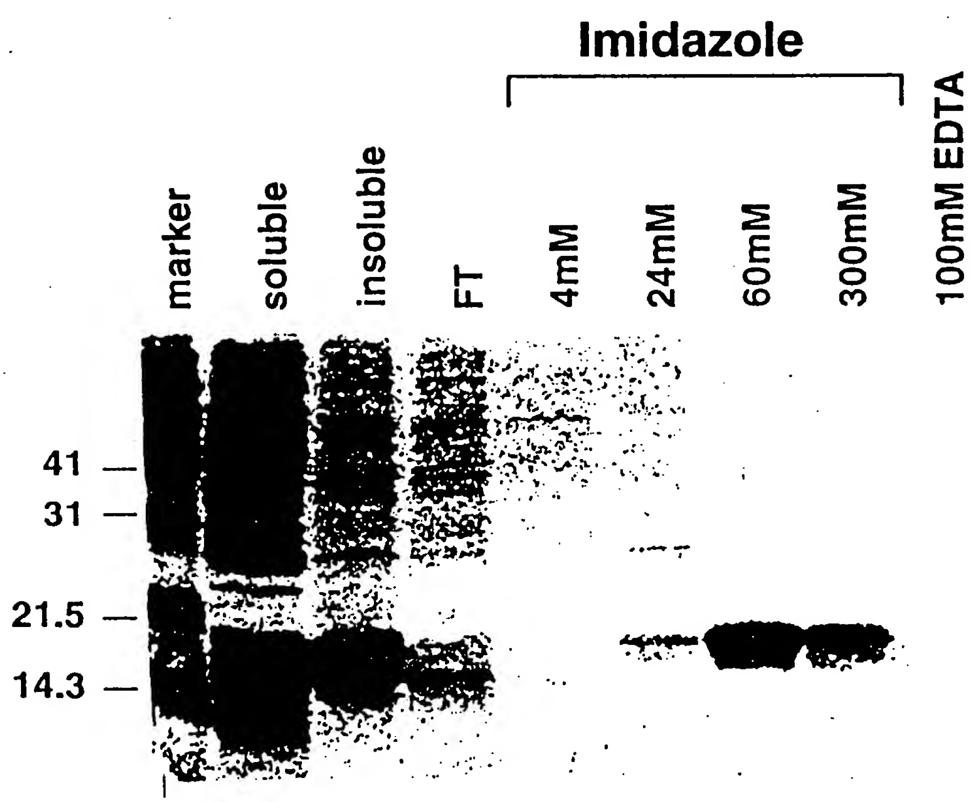

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Figure 28

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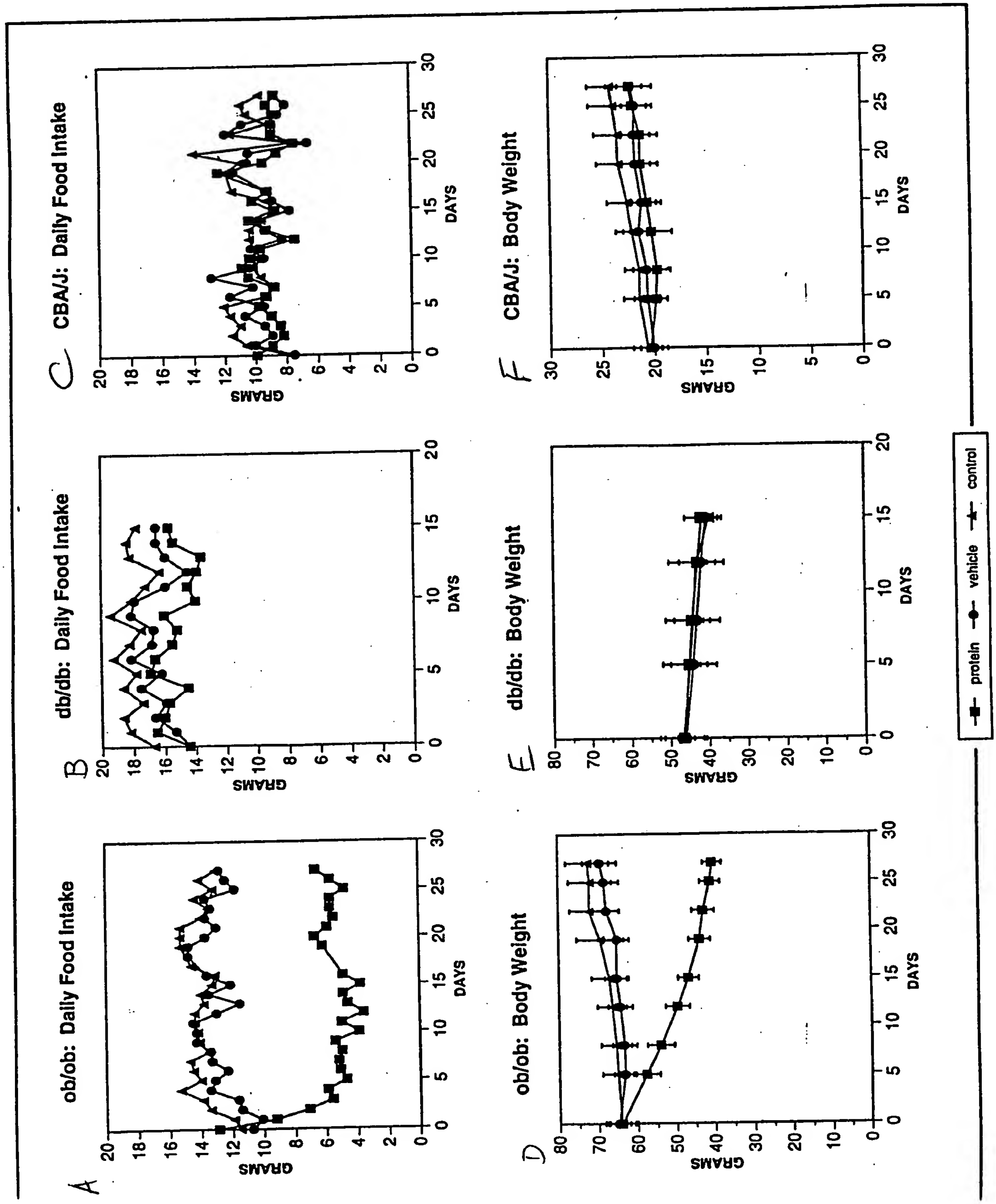

08/485943

Figure 29A

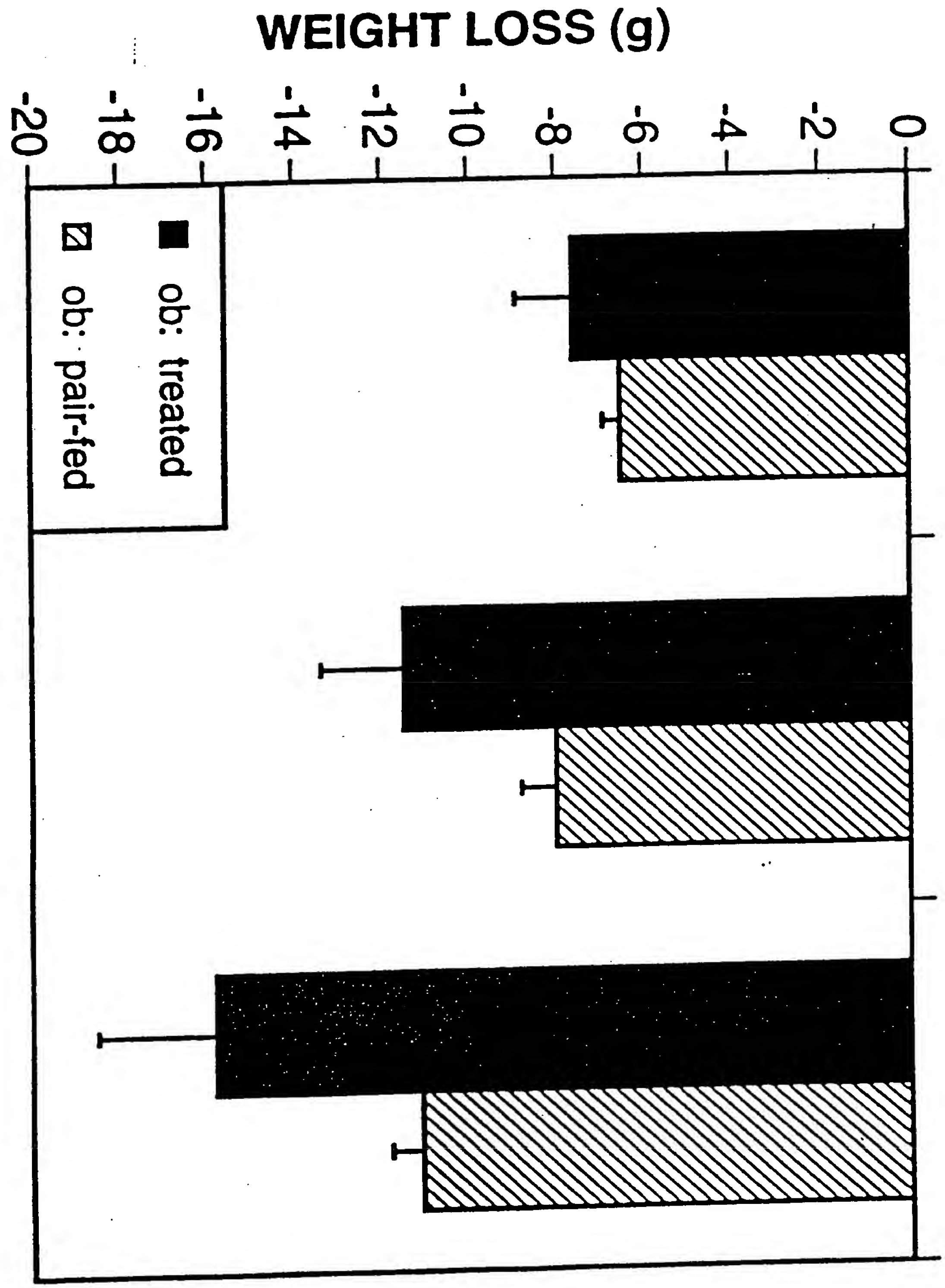

Figure 29B

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Figure 29C

08/485943

Figure 30

Wt

db/db

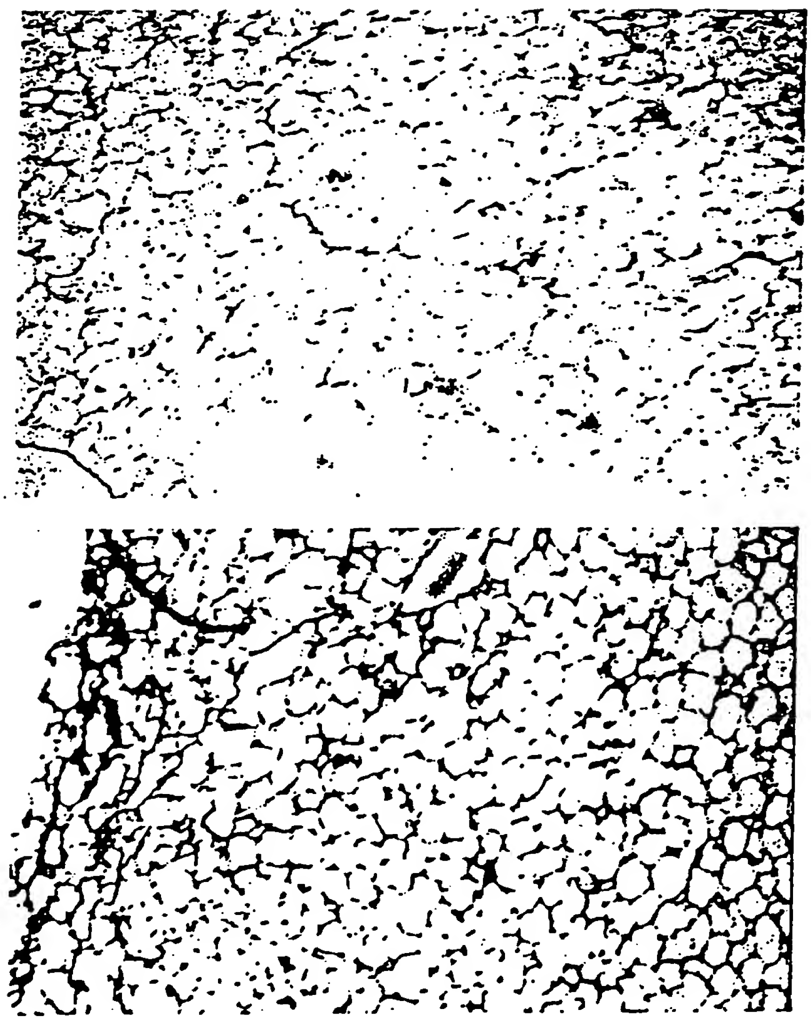

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Figure 31

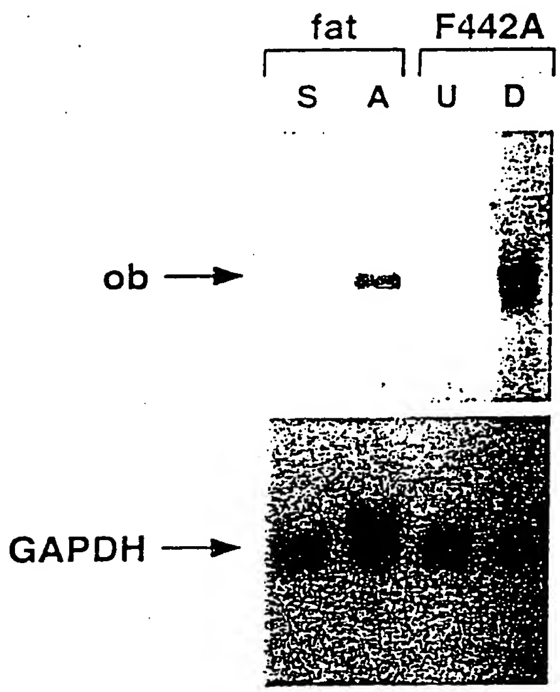

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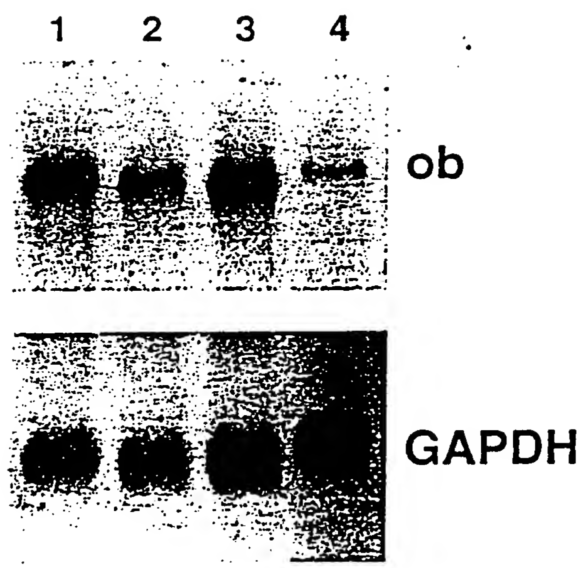
Figure 32A



08/485943

Figure 32 B

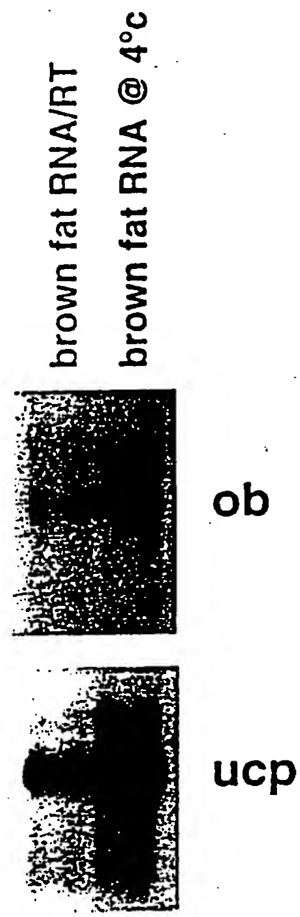


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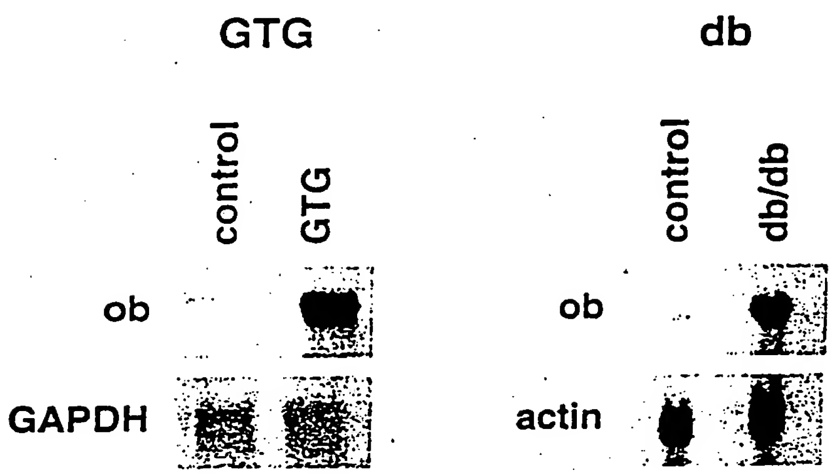
Figure 33



08/485943

Figure 34

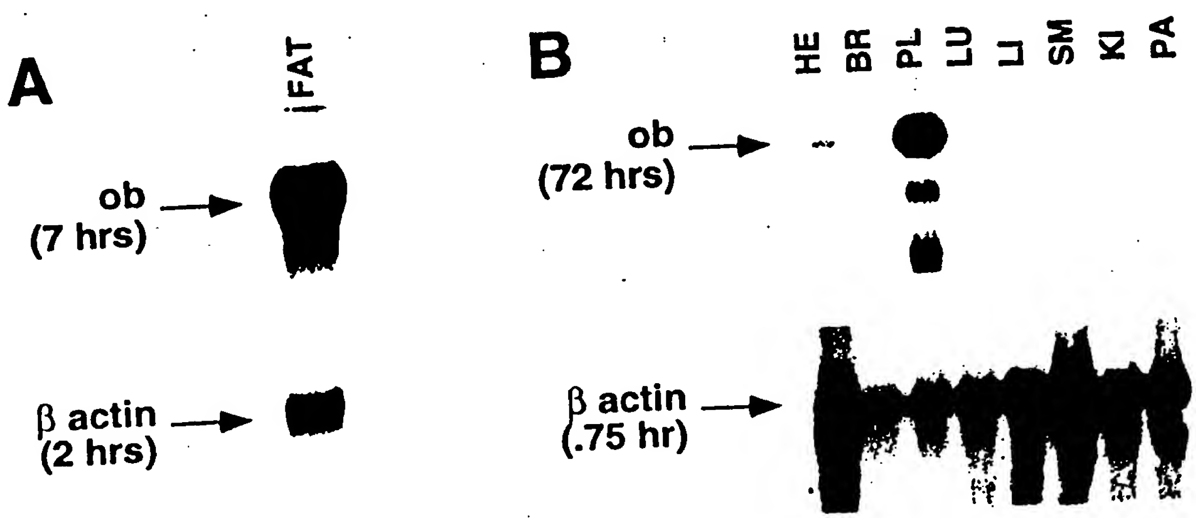


Figure 35

08/485943